# Pediatric Pulmonology Year in Review 2014: Part 2

***Pediatric Pulmonology* Year in Review 2014: Part 2**

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## Introduction

Our discipline and our journal cover an extremely broad range of research and scholarly topics related to children's respiratory disorders. To better meet the needs of our readership for updated perspectives on the rapidly expanding knowledge in our field, we will summarize the past year's publications in our major topic areas, as well as selected publications in these areas from the core clinical journal literature outside our own pages. A previous review (Part 1) summarized papers published in 2014 relevant to asthma, diagnostic testing/endoscopy, sleep and breathing disorders, respiratory complications of neuromuscular disorders, and rare lung diseases. The current review covers articles on neonatal lung disease, pulmonary physiology, and respiratory infection.

## Neonatal lung disease and bronchopulmonary dysplasia (BPD)

### *BPD pathogenesis, pathophysiology and biomarkers*

There is continued effort to understand the pathophysiology of modern-day BPD in preterm infants, which is a predisposing condition to adverse neurodevelopmental outcome as well as life-long respiratory system effects. The relatively wide variation of BPD incidence in NICUs suggests complex interaction of host factors and clinical care practices.

In a large epidemiologic study from the Swedish Birth Register, Eriksson et al.[1] reported that preeclampsia was a strong risk factor for BPD; no increased risk was associated with maternal chronic inflammatory diseases or use of anti-inflammatory drugs, and maternal diabetes appeared to decrease BPD risk. The authors concluded that impaired angiogenesis may contribute to BPD risk. Maternal factors including diabetes may adversely affect fetal lung development. In a diabetic rat model, Koskinen et al.[2] observed that maternal diabetes and hyperoxia combine to induce fetal lung

remodeling, delaying alveolarization. Genetic factors are being explored through genome-wide analyses, with some SNPs for known pathways and some novel risk-associated SNPs identified[3].

PH is a significant complication of prematurity and is associated with severe BPD[4]. Del Cerro and colleagues reviewed the course of pulmonary hypertension in a series of infants with BPD. At median follow-up of 35 months, 22 of 29 patients had been treated with PH drugs, 8 (26%) had died, and there was a high incidence (66%) of cardiovascular anomalies including aortopulmonary collaterals, pulmonary vein stenosis, and PDA, underscoring the need for definitive diagnosis of the etiology of PH. One of the plausible pathways identified involves angiogenesis, consistent with the so-called 'vascular hypothesis' of BPD pathogenesis. Along these lines, Zhang et al.[5] reported evidence supporting the predictive value of N-terminal pro-B-type natriuretic peptide (NT-proBNP), a widely used marker for pulmonary hypertension (PH) in adults, for readiness for extubation in mechanically ventilated preterm infants, and Kalra et al.[6] reported that elevated plasma BNP > 24.4 pg/mL at 36 weeks post menstrual age or at discharge home was a sensitive marker for BPD. Effects on the pulmonary vascular system were also suggested by Castro et al.[7] , who observed that the expression of angiotensin-converting enzyme (ACE) in lung endothelium is largely absent from the post-mortem lungs collected from children with BPD. Since angiotensin can affect angiogenesis in other systems, the authors speculate that lack of ACE expression could contribute to the development of BPD.

Oxidative stress is thought to be a common pathway mediating alveolar and vascular lung damage in preterm infants exposed to hyperoxia. In order to determine if limiting initial oxygen exposure could be done safely, investigators conducted a randomized trial of initial oxygen treatment ($F_IO_2$ = 35% v. 60%) during resuscitation of preterm infants, and found no impact on BPD[8]. In a preterm lamb model, combining surfactant with antioxidants superoxide dismutase and catalase mitigated tissue oxidative stress[9]. Oxidative stress and hypoxia contribute to pulmonary vascular remodeling, a feature common to both persistent pulmonary hypertension of the newborn and PH that complicates BPD.

Awad et al.[10] showed that hypoxia-induced catalase expression pathways in pulmonary artery smooth muscle cells is insufficient to protect pulmonary artery smooth muscle cells from hypoxia-induced lipid peroxidation. In an experimental rat model study, microRNA 26-a was noted to regulate surfactant protein expression by type II airway epithelial cells[11].

Pulmonary hypoplasia is typically complicated by PH, and is associated with high perinatal mortality. Its clinical diagnosis relies on relatively imprecise measures of lung expansion obtained by radiography as well as assessments of lung mechanics. At autopsy, the ratio of lung weight to body weight is typically used, but this measurement may be confounded by intra-alveolar lung liquid. De Paepe et al.[12] measured postmortem lung volumes, which would be unaffected by alveolar edema, and body weights in preterm and term infants at risk for pulmonary hypoplasia, and were able to determine age-specific lung volume/body weight reference values.

*Prevention and treatment of BPD and neonatal lung disorders*

Specific treatments or prevention strategies for BPD have been elusive. Wide variation in BPD incidence suggests multiple factors at play. Since mechanical ventilation is one such factor, investigators have pursued less invasive administration of treatments previously administered exclusively via the endotracheal route. In a randomized multicenter trial, inhaled nitric oxide in non-intubated preterm infants was safe but did not significantly reduce BPD risk[13]. However, combination of inhaled NO with vitamin A supplementation did have significant benefit[14].

Since pulmonary hypoplasia has been implicated in severe BPD, investigators have pursued cell-based therapies using progenitor cells that have yielded promising results in animal models, apparently via paracrine effects (see [15] for review ). In this same vein, a phase I trial of intratracheal allogeneic human umbilical cord blood (hUCB)-derived mesenchymal stem cell (MSC) transplantation in a small

group of 25-week gestation preterm infants yielded lower markers of inflammation and reduced BPD severity[16]. Anti-inflammatory treatment with corticosteroids is known to have a beneficial effect on the course of lung disease in preterm infants at risk for BPD, but is associated with significant side effects which limit use. Masood et al.[17] used a selective COX-2 inhibitor in neonatal rats to prevent neutrophil influx and reduce hyperoxia-induced lung injury, suggesting that non-steroid anti-inflammatory approaches - e.g., chemokine, chemokine receptor blockade - may be useful, as has been previously demonstrated by this research group and others who have targeted neutrophil and macrophage influx using similar model systems. Kahveci et al.[18] reported their retrospective experience with the prostacyclin analog inhaled iloprost, and sildenafil, in treatment of PPHN. They found that treatment with iloprost achieved a more rapid response and avoided systemic hypotension. The authors hypothesize that iloprost is safer and more effective (time to clinical response, duration of mechanical ventilation) than sildenafil, but this conclusion will require a direct comparison in a randomized, controlled trial.

The optimal timing and less-invasive methods of delivery of surfactant to preterm newborns are ongoing areas of investigation[19]. Minocchieri et al.[20] reported a series of aerosol experiments suggesting that nebulization of surfactant (vs. conventional direct instillation) may be a viable alternative, based on the physical characteristics of the nebulized material. The routine use of surfactant itself has come into question recently. The American Academy of Pediatrics Committee on the fetus and newborn published a policy statement indicating that continuous positive airway pressure started at or soon after birth with subsequent selective surfactant administration may be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants[21].

Volume-targeted ventilation was found in a meta-analysis to reduce BPD risk and other complications of premature birth, compared to pressure-limited ventilation strategies[22]. Noninvasive ventilation techniques are of increasing interest in neonatal medicine and may reduce BPD risk

compared to intubation with mechanical ventilation[23]. Stern et al.[24] reported a pilot clinical study to test the performance of bi-level nasal CPAP coupled with the Graseby capsule, a pneumatic device designed to detect infant breathing movements. They found that subxiphoid capsule placement achieved the best synchrony with respiratory movements. Shi et al.[25] reported a randomized controlled trial in which infants with RDS were supported with nasal intermittent positive pressure ventilation (NIPPV) vs. nasal CPAP; significantly fewer NIPPV treated infants (11%) required intubation and mechanical ventilation, compared to NCPAP (21%).

Placement of gastrostomy tubes (GT) (with or without Nissen fundoplication) to promote growth, address feeding difficulties, or limit pulmonary aspiration is common in infants with BPD. Recently, non-invasive oral-motor interventions have been assessed to determine if they can successfully address feeding problems. In order to determine the benefit of GT ± Nissen fundoplication on outcomes in children with BPD, McGrath-Morrow and colleagues conducted a retrospective review of 398 infants with BPD. They reported that infants with GT were more likely to have birth weights <10 %ile, to be discharged on supplemental oxygen, and to have more rehospitalizations, but no difference in signs of respiratory difficulty, according to caregiver questionnaire, than comparable BPD infants without GT[26]. As the authors pointed out, it cannot be determined that GT placement had any effect on BPD recovery in this retrospective analysis.

**Pulmonary physiology**

Race and ethnicity impact spirometric indices and interpretation of this data; therefore, choosing proper reference equations is critical. An interesting report by Wolff and colleagues[27] describes spirometry data in a population of normal children in Madagascar, who have diminished forced vital capacity (FVC) and forced expired volume in 1 second ($FEV_1$) compared to European[28] and

African[29] reference data. The authors speculate that genetic, environmental and socioeconomic factors may explain these differences. The GLI-2012 reference equations represent international data from Caucasians, African Americans and Asians, thus may not be appropriate for the African population. Given this, reference data such as those generated by Wolff and colleagues are important. Quanjer and Weiner[30] compared the interpretation of spirometry data, in a clinically and racially heterogeneous patient population at Children's Hospital of Pittsburgh, using the GLI-2012 prediction equations, compared to other published reference equations. Interpretation of the results was comparable between GLI-2012 and Wang and Hankinson references. However, interpretation differed when compared to Knudson, Polgar, or Zapletal. Hoo et al.[31] reported that both full term and premature nonwhite infants had lower forced expired volume at 0.5 seconds ($FEV_{0.5}$) and FVC at 12 months post-term age compared to white infants, highlighting the importance of ethnicity in interpretation of infant lung function as well as that in older children. Further, $FEV_{0.5}$ and forced expiratory flows in the extremely premature infants were diminished compared to preterm controls and this finding was more prevalent in those with bronchopulmonary dysplasia.

Lodge et al.[32] reported data from the Melbourne Atopy Cohort Study to shed further light on lung function sequelae of early childhood wheezing phenotypes. In children at high risk for allergy followed from birth, persistent wheeze phenotypes in childhood were associated with reduced $FEV_1$ values through adolescence. Intermediate-onset wheezers showed irreversible airflow limitation by 18 years, while early transient wheeze had no respiratory health sequelae by age 18.

Infant lung function (ILF) testing, while providing key data for clinical research, has had variable usage for clinical purposes. In a survey of international ILF practices, Peterson-Carmichael et al.[33] reported that ILF is less commonly used for clinical management in North America than in Europe and other continents. The need for sedation and time intensive nature of the testing were cited as factors limiting use. Using the Copenhagen Prospective Study on Asthma in Childhood 2000 birth cohort,

Kreiner-Moller et al.[34] studied the association of genetic variants previously associated with low lung function in adults, with infant lung function (raised-volume thoracoabdominal compression technique) and lung function development until age 7 years. There was no association of these genetic variants with lung function at 1 month, but a genetic variant associated with lung function in adults was associated with reduced forced expiratory flows at 50% of FVC ($FEF_{50}$) at 7 years of age and with increased bronchial responsiveness at age 7 years, suggesting that there is a window of opportunity for interventions targeting these genetic factors in early childhood.

Alternative, less effort-dependent lung function testing modalities in children are being refined. The multiple breath washout technique, a tidal breathing measure that uses an inert gas to assess ventilation inhomogeneity, has been shown to be sensitive to early disease in cystic fibrosis, and European Respiratory Society/American Thoracic Society guidelines were published in 2013 for the school age child[35]. Coutier and colleagues[36] compared results of specific airway resistance (sRaw) testing using the panting method compared to the tidal breathing method, in school age children; the panting method appeared to be more reliable. An interesting study used electric impedance tomography to assess ventilation distribution in spontaneously breathing infants and children. Findings revealed variability in the relationship between dependency and relative ventilation[37]. This challenges the dogma that non-dependent lung regions are better ventilated in children.

Lung function in specific disease or high-risk populations may be relevant for prognosis and clinical care. Lin et al.[38] described spirometry results in 35 children with mucopolysaccharidoses, showing that the majority had evidence for small airway obstruction, and about half had evidence of restriction. Chest CT scans were reported to correlate with lung function abnormalities in pediatric sarcoidosis patients; thereby, potentially allowing a reduction in the number of CT scans required for follow-up[39]. In healthy adolescents, obesity was reported to be associated with lung function abnormalities, with a negative relationship between BMI and percent predicted functional residual

capacity (FRC), residual volume (RV), and $FEV_1/FVC$ [40]. Diminished lung volumes occurred in those with elevated BMI, and adiposity measures included body mass index (BMI), percent body fat (PBF), and waist circumference (WC). Forno et al.[41] showed links among these adiposity measures, atopy, asthma control, and lung function changes in Puerto Rican asthmatics. Prenatal bisphenol A exposure, a prevalent endocrine disrupter, was demonstrated to be linked to wheezing and reduced $FEV_1$ at age 4 years in a birth cohort study[42].

Prognostically and therapeutically important physiologic data may be obtained in children with neuromuscular disorders. Felix et al. [43] reported that inspiratory muscle training in children with ataxia telangiectasia (A-T), a genetic disorder involving neuromuscular weakness and impaired cough, resulted in significant improvements in both lung volume and quality of life. In another retrospective report on children with A-T, the majority of patients less than 15 years of age who died of respiratory causes had *S. aureus, S. Pneumoniae,* or *H. influenzae* cultured from respiratory secretions; while older patients had a high prevalence of *P. aeruginosa*[44]. To achieve lung volume recruitment in patients with neuromuscular weakness, voluntary breath stacking has been a useful technique. Jenkins et al.[45] reported a careful study of the effects of involuntary breath stacking maneuver in 6 children with muscular dystrophy, and documented improvements in minute ventilation, suggesting that this technique might be useful in children unable to voluntarily cooperate. Finkel and colleagues[46] provided striking data demonstrating the feasibility and safety of testing respiratory muscle strength in infants with spinal muscular atrophy type I.

**Respiratory infection**

While overall there has been progress in reducing childhood mortality worldwide, pneumonia remains the major cause of death in young children outside the neonatal period, especially in sub-

Saharan Africa and Asia[47]. Agweyu et al. reported that oral amoxicillin is not inferior to i.v. penicillin in the treatment of children age 2-59 months with WHO-defined severe pneumonia.

Respiratory manifestations of HIV infection are an important issue and were addressed in several important studies. In low- and middle-income countries, HIV infection continues to be a major risk factor for childhood pneumonia[48]. Theodoratu et al.[49] reviewed studies of pneumonia in HIV-infected children, highlighting the disproportionately high risk in this population. Pitcher and colleagues[50] reported a prospective study of 330 HIV-infected children in South Africa, in which chest x-ray findings were correlated with clinical and immunologic factors. More severe x-ray findings including confluent opacifications and nodules were associated with a 7-fold odds ratio for advanced clinical HIV disease.

Inequity in health outcomes is a major issue in children with chronic lung diseases. Singleton et al.[51] reported a study of factors associated with increased risk for chronic suppurative lung disease (CSLD), including bronchiectasis, among indigenous children from Australia, the US, and New Zealand. Like the overall indigenous population, these children had poor housing and socioeconomic status; but household crowding, prematurity and a history of early acute lower respiratory infections were associated with CSLD. Addressing these factors may help reduce CSLD in these at-risk children. In an interesting study comparing quality of life and other factors between CSLD and CF patients, Nathan et al.[52] concluded that growth outcomes and parental mental health are actually worse in children with CSLD than children with CF.

The investigation of aerosolized antibiotics for treatment of respiratory infection has continued, and the physicochemical effects on drugs of aerosolization are critical to understand. Kamalaporn et al.[53] reported an in vitro study in which nebulization of liposomal amphotericin B did not disrupt liposomes, which were promising results for its eventual use in children with Aspergillosis and other

fungal infections. *Acinetobacter* was treated successfully with inhaled colistin monotherapy (34 mg twice daily for an average of 9 days) in 8 premature infants in a report from Kang et al.[54] The infants ranged in age from 33-103 days, and in weight from 1470 to 3840 grams, and none had renal toxicity. The description of cough (wet vs. dry) may have implications for infection risk. Wurzel et al.[55] prospectively studied BALF characteristics among children undergoing bronchoscopy for cough, and those with wet cough had higher BALF neutrophilia and bacterial and viral infection than those with dry cough.

Honkinen et al.[56] provided long-term imaging (MRI) and functional followup of 26 children with empyema. While spirometry was normal in 80%, 92% had MRI abnormalities, mostly pleural scarring, though the physiologic significance may be minor. Differentiating bacterial from viral pneumonia for purposes of decisions about antibiotics is challenging. Torres et al.[57] carried out a trial in which children age 3-60 months with acute pneumonia in an outpatient setting were randomized to routine management vs. use of a bacterial pneumonia predictive score. The group managed according to the standardized score received less antibiotics, but the clinical outcomes did not differ between groups.

Respiratory syncytial virus (RSV) continues to be a prominent and costly cause of acute lower respiratory illness in children worldwide[58]. A household cohort study that used molecular RSV diagnostics revealed that school-going children in a household are the major source of infant RSV infection [59]. Rodriguez et al.[60] reported that risk factors for severe RSV disease in Colombia include age < 6 months, prematurity, congenital heart disease, and mixed RSV-adenovirus infection. A meta-analysis of studies assessing relation between vitamin D receptor polymorphisms and acute RSV bronchiolitis yielded only 3 eligible studies, but all three suggested a significant association between the *Fok*I allele and severe disease[61]. In treating RSV bronchiolitis, the use of epinephrine, albuterol and corticosteroids may be decreasing, but only modestly, following publication of practice guidelines highlighting lack of effectiveness of these agents[62] . The use of palivizumab in children with chronic lung conditions other

than prematurity remains a topic of debate, due to the paucity of controlled trials. Gaboli et al.[63] reported a Delphi study involving 48 Spanish experts, in which expert consensus favored the use of palivizumab in children up to 12-24 months of age with neuromuscular weakness, CF, ciliary disorders, tracheoesophageal atresia, bronchopulmonary malformations, and lung transplant recipients. Comparing acute and convalescent sera, Sande et al.[64] show that neutralizing antibody titers to RSV only rise if infants were 4 months or older at the time of natural RSV infection, suggesting that live RSV vaccination will not be effective before 4 months of age and that maternal vaccination will be required to protect very young infants.

Tuberculosis (TB) continues to be a worldwide problem. Walters et al.[65] reported data from a small series of children with complicated TB, in some of whom the addition of rapid PCR-based testing of BALF for *M. tuberculosis* gave added information of therapeutic importance. Garazzino et al.[66] reported a series of 9 pediatric patients age 6 months to 13 years, who were treated with moxifloxacin 10 mg/kg/day as part of an anti-TB multiple drug regimen. Clinical outcomes were good, and one patient (age 6 years) developed arthritis, and another (age 3 years) had liver toxicity. One of the potential complications of pulmonary tuberculosis (TB) in children is compression of central airways by enlarged mediastinal lymph nodes. Andronikou and co-authors[67] hypothesized, based on a study of CT findings in children with TB, that mediastinal shift from right lung volume loss is associated with compression of the left main stem bronchus due to narrowing of the pulmonary artery bifurcation angle.

*Mycoplasma pneumoniae* is a common acute infection in Chinese children, and in some cases is refractory to macrolide treatment. In a randomized controlled trial, children with refractory mycoplasma received either intravenous azithromycin (10 mg/kg/day) alone or azithromycin plus oral prednisolone (2 mg/kg/day) for 5 days[68]. Clinical outcomes of dyspnea, resolution of radiographic changes, duration of hypoxemia, and fever were all better in the corticosteroid group.

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